Neoadjuvant Breast Cancer Therapy

A Surgical Perspective

Jane O'Brien
Breast Surgeon

TOPICS

- Evolving Indications for Neoadjuvant Chemotherapy (NAC)
- Utilisation Trends
- Practical Issues
- Surgical De-escalation Options
- 2 year Personal Practice NAC Audit 2017-2019

Potential Indications for NAC have Broadened

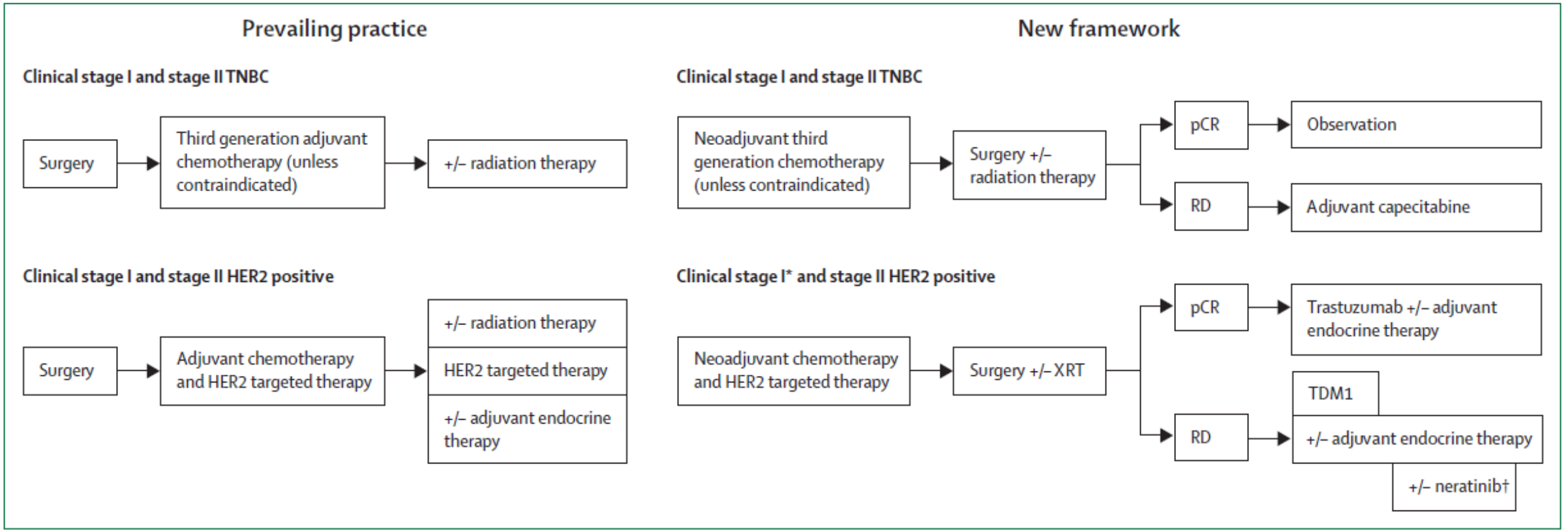
Before:

- Locally Advanced Breast Cancer (LABC)
- "Inoperable" Inflammatory Breast Cancer (IBC)
- High burden of disease (N2/3)

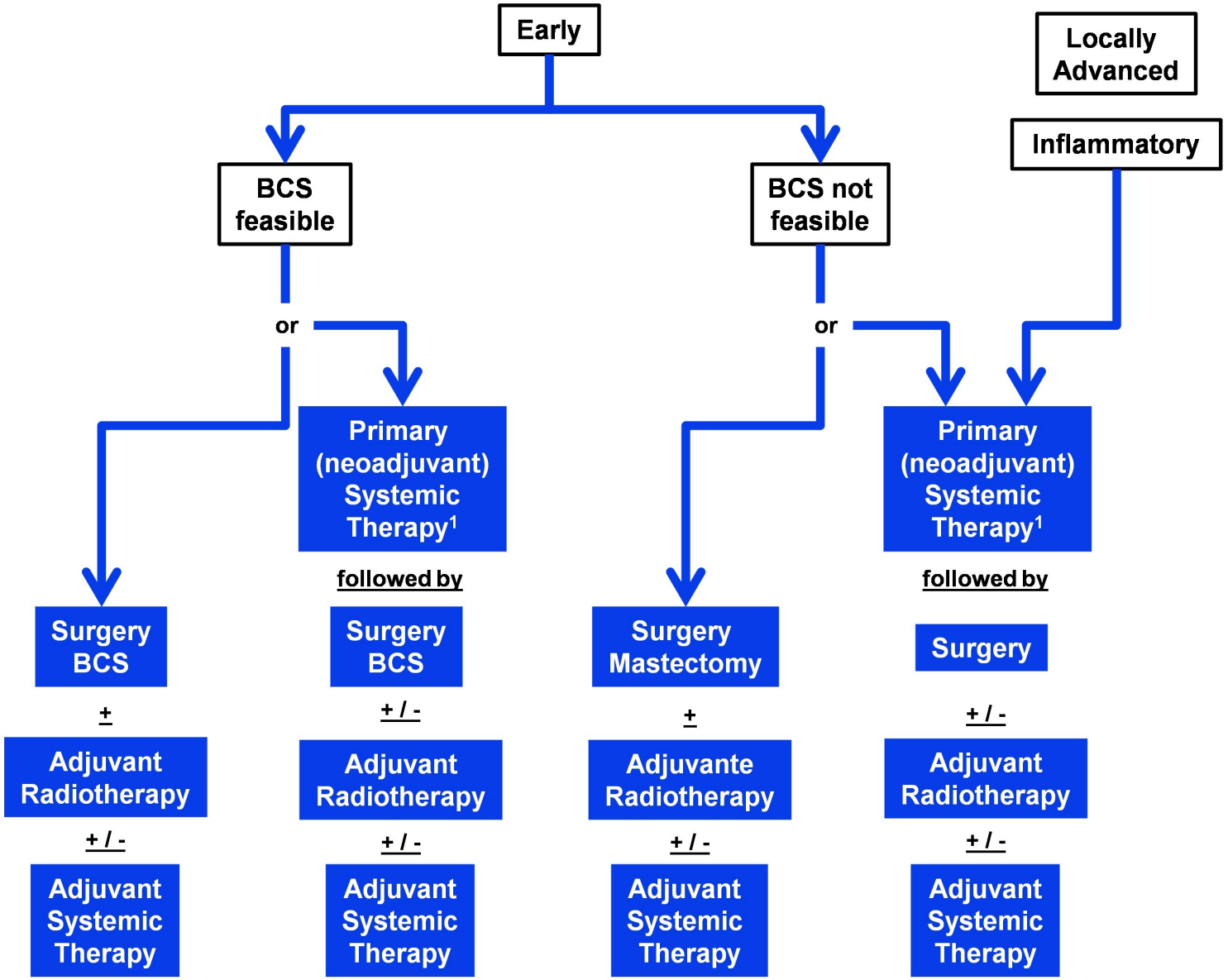
Now (in addition):

- Early, operable breast cancer

- Alter extent of surgery- breast +/- axilla
- Assess/evaluate in vivo response to therapy
- Adjusting neoadjuvant therapy
- Prognostic information
- Consider Post-neoadjuvant treatment and the management of residual disease after NAC



Lancet Oncology, 2019


Early
Locally Advanced
Inflammatory
BCS feasible
BCS not feasible
or
or
Primary (neoadjuvant) Systemic Therapy1
Primary (neoadjuvant) Systemic Therapy1
followed by
followed by
Surgery BCS
Surgery BCS
Surgery Mastectomy
Surgery
+
+ / -
+
+ / -
Adjuvant Radiotherapy
Adjuvant Radiotherapy
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+ / -
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Adjuvant Systemic Therapy
Adjuvant Systemic Therapy
Adjuvant Systemic Therapy
Adjuvant Systemic Therapy

Advantages of NAC

- Potential Surgical De-escalation
- Breast- Improved cosmesis in the already or borderline conservable/ increased BCS
- Axilla- reduction in ANC (not all subtypes)
- Surgical Planning
- Can commence immed
- Prehab-to optimise conditioning prior to surgery– lose weight, exercise, stop smoking, optimise diabetic control
- Genetic Testing results avail presurgery

Advantages of NAC

- Assess/evaluate in vivo response to therapy- access to novel agents eg Chariot
- Prognostic information
- Adjusting systemic therapy
- Plastic Surgical Planning
- Special circumstances eg pregnancy
- Consider post-neoadjuvant treatment and the management of residual disease after neoadjuvant treatment
- May potentially allow de-escalation XRT (pending outcome NSABP B-51/RTOG 1304)
- Avoids delaying commencement of adjuvant chemo if surgical complications

Disadvantages of NAC

- Time Intensive- for patients and specialists
- More expensive-more and lengthier consultations, more investigations/interventions/often more costly drugs
- More visits- initial diagnostic work up, usually 3 visits during treatment (all half hour appointments), then usual peri/post op care
- More interventions- clip placement
- More breast imaging- check imaging ? incl repeat MRI

Disadvantages of NAC

- Don't have genetic test results to choose initial chemo regimen
- Fertility interventions may be compromised
- Small risk of disease progression (3%, Caudle et al, Ann Surg Onc, 2011)
- Reduced time between surgery and radiation (only a potential issue with PMRT following implant based breast reconstruction)
- May have increased chance ANC in ER/PR+/HER2-ve (Boughey et al Ann Surg Onc, 2018)

Clinical benefits and potential concerns associated with neoadjuvant treatment for early breast cancer

	Benefits	Potential concerns
Impact on surgery	• Downstage tumours to permit breast-conserving surgery rather than mastectomy [4–6], improving cosmetic outcomes. • De-escalate surgical treatment of the axilla [7]. • Provide time for germline mutation test results (i.e. *BRCA1/2*) that may influence surgical plan.	• Cancer may progress and become inoperable (a rare event with appropriate monitoring of response). • Reduced window of opportunity for fertility preservation [8]. • Increasing tumour response may not achieve a reduction in mastectomy rates, regardless of downstaging and effectiveness of therapy regimen [9,10]. • Increased locoregional recurrence rates in patients who do not undergo surgery after neoadjuvant treatment [11].
Disease information and monitoring	• Provide individualised post-treatment prognostic information (e.g. pathological complete response, residual cancer burden) for management decisions. • Permits clinicians to monitor response to therapy at an early stage; potentially allowing time and flexibility to switch therapies if patients do not respond [12,13].	• Potential loss of staging information. • Potential for over-treatment, if decision is based on incomplete information (e.g. size of lesion is overestimated because of associated ductal carcinoma *in situ* seen radiologically). • Potential for under-treatment if therapy is stopped or changed mid-course [14]. • Limited evidence base to guide adjuvant radiotherapy decisions or management of patients with residual disease.

Clinical Oncology, 2017

Australian Government
Cancer Australia

Influencing best practice in breast cancer

8 Appropriate to consider the pre-operative use of chemotherapy or hormonal therapy (systemic, neoadjuvant therapy) informed by hormone and HER2 receptor status, for all patients where these therapies are clinically indicated.

CONTEXT

National and international guidelines recommend that all patients with early breast cancer be tested for hormone and HER2 receptor status. For many patients with operable breast cancer whose hormone and HER2 receptor status is known, chemotherapy or hormone/endocrine therapy given before surgery (neoadjuvant) has a number of benefits compared to surgery as the first treatment.

Neoadjuvant therapy can shrink the cancer, improving the chance of achieving breast conserving surgery rather than mastectomy. It also allows for an early evaluation of the response of the cancer to therapy, enabling ineffective treatment to be discontinued, and alternate treatments to be considered.

Studies have shown that giving systemic treatment either before or after surgery is equally as effective, in terms of overall survival and disease progression.

VALUE TO PATIENTS

Consideration of systemic neoadjuvant therapy in eligible patients based on hormone and HER2 receptor status, with consideration of tumour size, grade and nodal involvement, by the multidisciplinary team and discussion with patients will enable patients to realise the potential benefits of this approach.

SUPPORTING EVIDENCE

Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of Oncology. 2015;26(8):1533-46.

Kaufmann M, von Minckwitz G, Mamounas EP, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Annals of Surgical Oncology. 2012;19(5):1508-16.

Leal F, Liutti VT, Antunes dos Santos VC, et al. Neoadjuvant endocrine therapy for resectable breast cancer: A systematic review and meta-analysis. Breast. 2015;24(4):406-12.

Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. British Journal of Surgery. 2007;94(10):1189-200.

Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Journal of Clinical Oncology. 2013;31(31):3997-4013.

St Gallen Guidelines 2019

Table 1. Changes in panel recommendations since 2017

Global perspectives	Worldwide, outcomes for early-stage breast cancer are improving owing to successful screening programs and improved multidisciplinary care. These advances are often associated with treatments which carry less morbidity than treatments in the past.
	Shared clinical decision making is essential when caring for individual breast cancer patients. In particular, patients should be informed about the expected magnitude of benefit of interventions in their individual case when deciding which therapies to pursue
	There are substantial variations around the world in availability of important treatments for breast cancer. Stakeholders should work to ensure that patients have access to essential treatments that improve survival for women with breast cancer
Surgical management	'No ink on tumor' is a sufficient surgical margin in most cases of primary invasive breast cancer, including patients with lobular breast cancer or extensive intraductal components, and after resection of residual palpable or imaging abnormalities following NST
	ALND can be omitted after SLNB with one to two positive lymph nodes after mastectomy if RNI was planned. ALND can be omitted after SLNB with one to two positive lymph nodes following breast conserving surgery for tumors larger than 5 cm if WBI is planned.
Neoadjuvant therapy	Neoadjuvant systemic therapy (NST) is the preferred initial approach in women with stage 2 or 3, HER2-overexpressing or triple-negative breast cancer
	NST increasingly enables selected women to avoid axillary dissection surgery, sparing women loss of function and lymphedema
	NST increasingly enables tailored approaches to therapy in TNBC and HER2-positive breast cancer that can improve long-term outcomes for women with breast cancer
ER+ adjuvant therapy and genomic signatures	More women with ER-positive breast cancer and limited involvement of axillary lymph nodes may avoid adjuvant chemotherapy
	More premenopausal women with intermediate/high risk ER-positive breast cancer should consider ovarian function suppression
	Genomic signatures may inform treatment recommendations for women with ER-positive breast cancers and limited nodal involvement
	Clinical-risk stratification provides prognostic information that, when added to the 21-gene recurrence score, could be used to identify women younger than age 50 women who may benefit from more effective therapy than tamoxifen alone
HER2+ and TNBC adjuvant therapy	Women with stage 2 or 3 HER2-positive breast cancer should consider adding pertuzumab in addition to trastuzumab
	Women with HER2-positive and residual tumor after NST should receive trastuzumab emtansine therapy in the adjuvant setting
	Women with triple-negative breast cancer and residual tumor after NST should consider capecitabine in the adjuvant setting
Adjuvant bisphosphonates	Bisphosphonates should be standard adjuvant therapy for postmenopausal patients with breast cancers

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Invasive Breast Cancer

WORKUP PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

CLINICAL STAGE	WORKUP[a]
T0-4,N1-3,M0[pp] or T2-4,N0,M0[pp]	• History and physical exam • Diagnostic bilateral mammogram; ultrasound as necessary • Pathology review[c] • Determination of tumor ER/PR status and HER2 status[d] • Genetic counseling if patient is at risk[e] for hereditary breast cancer • Breast MRI[f] (optional), with special consideration for mammographically occult tumors • Counseling for fertility concerns if premenopausal; pregnancy test in all women of childbearing potential[g] • Assess for distress[h] • Additional studies consider:[i] • CBC • Comprehensive metabolic panel, including liver function tests and alkaline phosphatase • Chest diagnostic CT with contrast • Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast • Bone scan or sodium fluoride PET/CT[j] (category 2B) • FDG PET/CT[k,l] (optional)

POTENTIALLY OPERABLE DISEASE: ADJUVANT THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY

- Complete planned chemotherapy regimen course if not completed preoperatively.
- Consider adjuvant capecitabine in patients with triple-negative breast cancer and residual invasive cancer following standard neoadjuvant treatment with taxane-, alkylator-, and anthracycline-based chemotherapy.

and

- Adjuvant radiation therapy[s] is based on maximal disease stage from prechemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results.
  - Post mastectomy:[s]
    - Strongly consider radiation to the chest wall + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk for clinical N1, ypN0.
    - For ANY positive axillary nodes after chemotherapy, radiation therapy as indicated to the chest wall + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk.
  - Post lumpectomy:[s]
    - Adjuvant radiation post-lumpectomy is indicated to the whole breast with or without boost to the tumor bed.
    - Strongly consider radiation to the whole breast + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk for clinical N1, ypN0.
    - For ANY positive axillary nodes after chemotherapy, radiation therapy as indicated to the whole breast + infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk.

and

- Adjuvant endocrine therapy,[cc] if ER-positive and/or PR-positive (category 1)

and

- If HER2-positive:
  - If no residual disease: Complete up to one year of HER2-targeted therapy with trastuzumab (category 1) ± pertuzumab. HER2-targeted therapy may be administered concurrently with radiation and with endocrine therapy if indicated.[uu]
  - If residual disease: Ado-trastuzumab emtansine (category 1) alone for 14 cycles. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy. HER2-targeted therapy may be administered concurrently with radiation and with endocrine therapy if indicated.[uu]

→ See Surveillance/ Follow-up (BINV-17)

Table 1 Factors for consideration in the utilization of NAC

NAC	Greater benefit	Less benefit
Tumour type	High grade	Low grade
	High Ki67	Low Ki67
	Luminal B	Luminal A
	Her2 positive, hormone-negative TNBC	Lobular subtype
Surgical advantage	Enable/improve BCS	BCS appropriate at diagnosis
	Enable IBR	IBR appropriate at diagnosis
	Reduce ALND	
Decision making	Genetic testing	Uncomplicated
	Surgical options	Radiotherapy plan uncertain
	Reconstruction options	IBR + PMRT?
Research	Access to clinical trials	–
	Tumour response to drug allowing biomarker discovery	
	Individualized therapy	
Other	Pregnancy	–

Read et al, ANZ J Surg, 2015

NAC Utilisation

	% of breast cancers overall undergoing NAC	% pts undergoing chemo who received NAC
USA 2003-2008	3.8	20% 2010-2015 (15.7 2010, 26.0% 2015)
Australia 2011-2016	4.43	
Personal Practice 2018	14%	30%

REVIEW ARTICLE

ANZJSurg.com

Utility of neoadjuvant chemotherapy in the treatment of operable breast cancer

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ORIGINAL ARTICLE

ANZJSurg.com

Neoadjuvant systemic therapy for breast cancer: the Westmead experience

Annelise M. Cocco,* David Messer,* Alexander Brown,* Nina Sriram,* Jenny Gilchrist,† Loma Al-Mansouri,‡ Richard Kefford,‡ Farid Meybodi,* James French,*§ Jeremy Hsu*‡ and Elisabeth Elder*§

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Ann Surg Oncol (2017) 24:1242–1250
DOI 10.1245/s10434-016-5733-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

National Trends in the Use of Neoadjuvant Chemotherapy for Hormone Receptor-Negative Breast Cancer: A National Cancer Data Base Study

Carlos A. Puig, MD[1], Tanya L. Hoskin, MS[2], Courtney N. Day, BS[2], Elizabeth B. Habermann, PhD[1,2,3], and Judy C. Boughey, MD[1]

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Factors associated with NAC use

- Younger age
- Pre-operatively known positive nodal status
- Increasing clinical tumour size

Personal Practice Jane O'Brien

Year	% of all breast cancer pts undergoing NAC
2013	4
2014	5
2015	4
2016	10
2017	9
2018	14
2019	14

Personal Practice 2018

Chemotherapy

- 45% pts overall underwent chemotherapy.
- 70% of these in the adjuvant setting
- 30% neoadjuvant (NAC) chemotherapy

Neoadjuvant Chemotherapy

- 14% breast cancer patients overall underwent (neoadjuvant chemotherapy-NAC) prior to surgery.
- 30% patients undergoing chemotherapy, received it in the neoadjuvant setting

- In 10% of the women undergoing NAC, the indication was LABC with either inflammatory breast cancer or skin involvement.

- The remaining 90% women had "operable" breast cancer at diagnosis, and neoadjuvant chemotherapy was undertaken in the context of a potentially "chemo-sensitive" subtype ie triple negative breast (TNBC) or HER2+ve.

- 86% of these women subsequently underwent successful breast conserving surgery.

Neoadjuvant Chemotherapy Use in Breast Cancer is Greatest in Excellent Responders: Triple-Negative and HER2+ Subtypes

Brittany L. Murphy, MD, MS[1,2], Courtney N. Day, BS[3], Tanya L. Hoskin, MS[3], Elizabeth B. Habermann, PhD, MPH[1,2,3], and Judy C. Boughey, MD, FACS[1]

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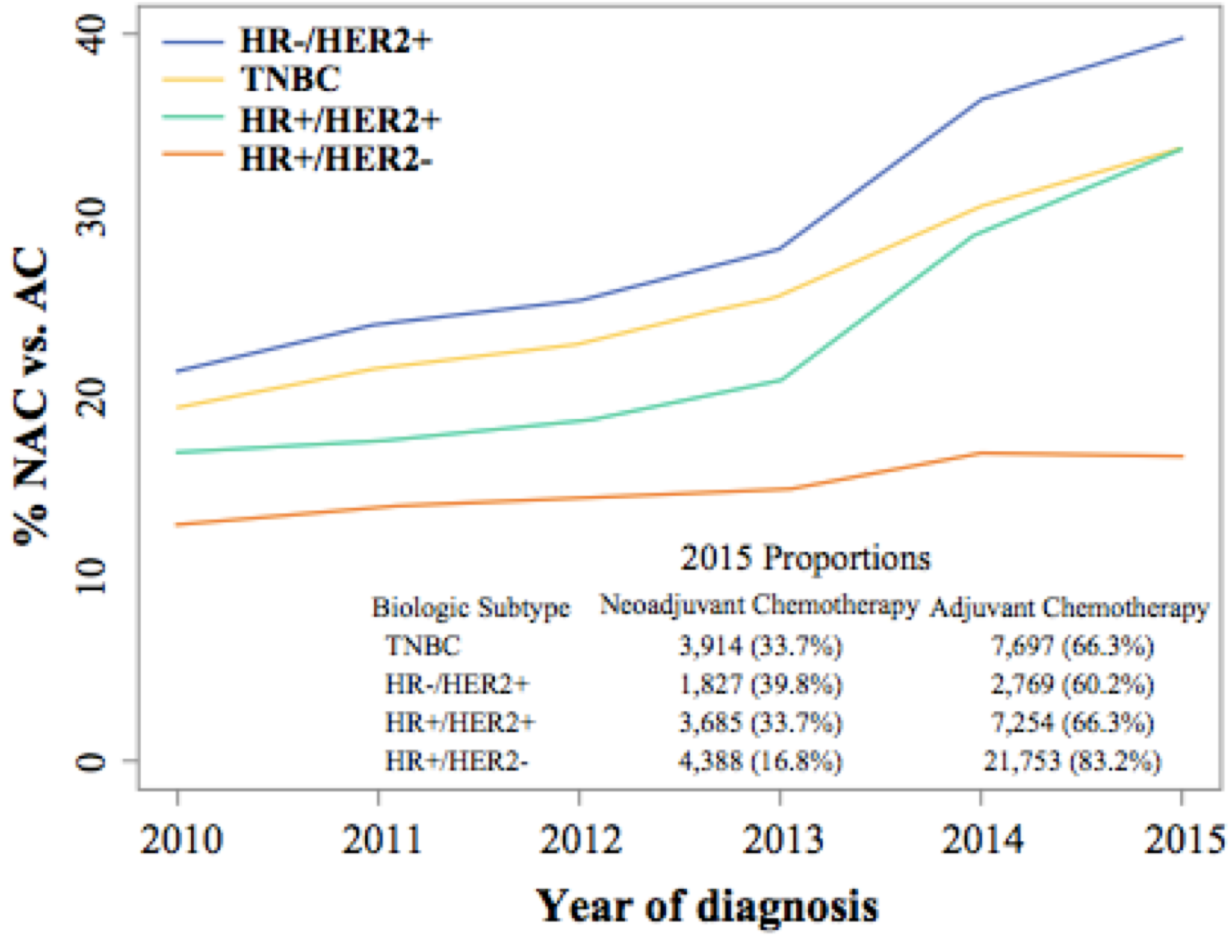

FIG. 1 Proportion of patients receiving neoadjuvant chemotherapy versus adjuvant chemotherapy, stratified by biologic subtype. *AC* adjuvant chemotherapy, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *NAC* neoadjuvant chemotherapy, *TNBC* triple-negative breast cancer

Ann Surg Onc, 2018

Neoadjuvant chemotherapy rates for breast cancer in Australia—"are we there yet?"

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Contributions: (I) Conception and design: PD Patiniott, B Fosh; (II) Administrative support: B Fosh; (III) Provision of study materials or patients: B Fosh, YH Lam; (IV) Collection and assembly of data: PD Patiniott, GY Wong, YH Lam; (V) Data analysis and interpretation: PD Patiniott, GY Wong, YH Lam; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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- BreastSurgANZ Audit data 2011-2016
- 4.43% underwent NAC
- 2011-3.08%
- 2016-6.65%

Table 2 Use of NAC in each of the states and territories in Australia

State	Total cases	NAC	% NAC
ACT	885	35	3.95
NSW	17,661	716	4.05
NT	242	13	5.37
QLD	11,400	468	4.11
SA	6,536	270	4.13
TAS	854	41	4.80
VIC	12,821	680	5.30
WA	5,358	246	4.59

Annals of Breast Surgery, 2019

Table 1 Incidence of early and locally advanced breast cancer, utilisation of NAC and utilisation of NAC in Australia from 2011 to 2016

Variable	2011	2012	2013	2014	2015	2016	Total
Early and locally advanced breast cancer in Australia	9,325	9,355	9,711	9,912	8,804	8,650	55,757
HER2 positive	1,122	1,160	1,201	1,231	1,061	980	6,755
TNBC	920	990	972	937	863	891	5,573
NAC, n (%)	287 (3.08)	332 (3.55)	370 (3.81)	407 (4.11)	498 (5.66)	575 (6.65)	2,469 (4.43)
Adjuvant chemotherapy, n (%)	4,253 (45.61)	4,400 (47.03)	4,505 (46.39)	4,241 (42.79)	3,764 (42.75)	3,687 (42.62)	24,850 (44.57)

TNBC, triple negative breast cancer; NAC, neoadjuvant chemotherapy.

Neoadjuvant Systemic Therapy for Breast Cancer: Factors Influencing Surgeons' Referrals

Eleftherios Mamounas, MD[1], Christine Poulos, PhD[2], Hans-Peter Goertz, MPH[3], Juan Marcos González, PhD[2], Amy Pugh, BA[2], and Vincent Antao, PhD[3]

[1]University of Florida Health Cancer Center–Orlando Health, Orlando, FL; [2]RTI Health Solutions, Research Triangle Park, NC; [3]Genentech Inc., South San Francisco, CA

- Study aimed to assess the influence of disease- and patient-related factors on surgeons' decisions to refer patients with early-stage breast cancer (EBC) for NAC
- More than half were "very likely" to refer EBC patients for NST based on anatomico-pathologic factors.
- Less than 50 % were "very likely" to do so when considering tumour phenotype factors.
- Tumour size and lymph node status were ranked highest in hypothetical patient scenarios.
- More than half of the respondents were unaware that findings have shown achievement of pathologic complete response (pCR) after NST to be associated with improved survival.
- Conclusions:
- Surgeons' decision to refer for NST is strongly driven by surgical management goals. Anatomicopathologic factors are more influential than tumour phenotype. However, no single disease or patient factor consistently drives the decision to refer for NST.
- Surgeons' awareness of the association between pCR achievement and longer survival could be improved.

Ann Surg Onc, 2016

Process

- Consideration NAC often starts even before the first consultation
- May discuss imaging/Core Bx in MDM prior to initial consultation
- Start framing the treatment sequencing discussion early
- Pt with confirmed diagnosis- aim to see with immuno
- T2/N1- Start discussion re sequencing of treatment if favourable subtype

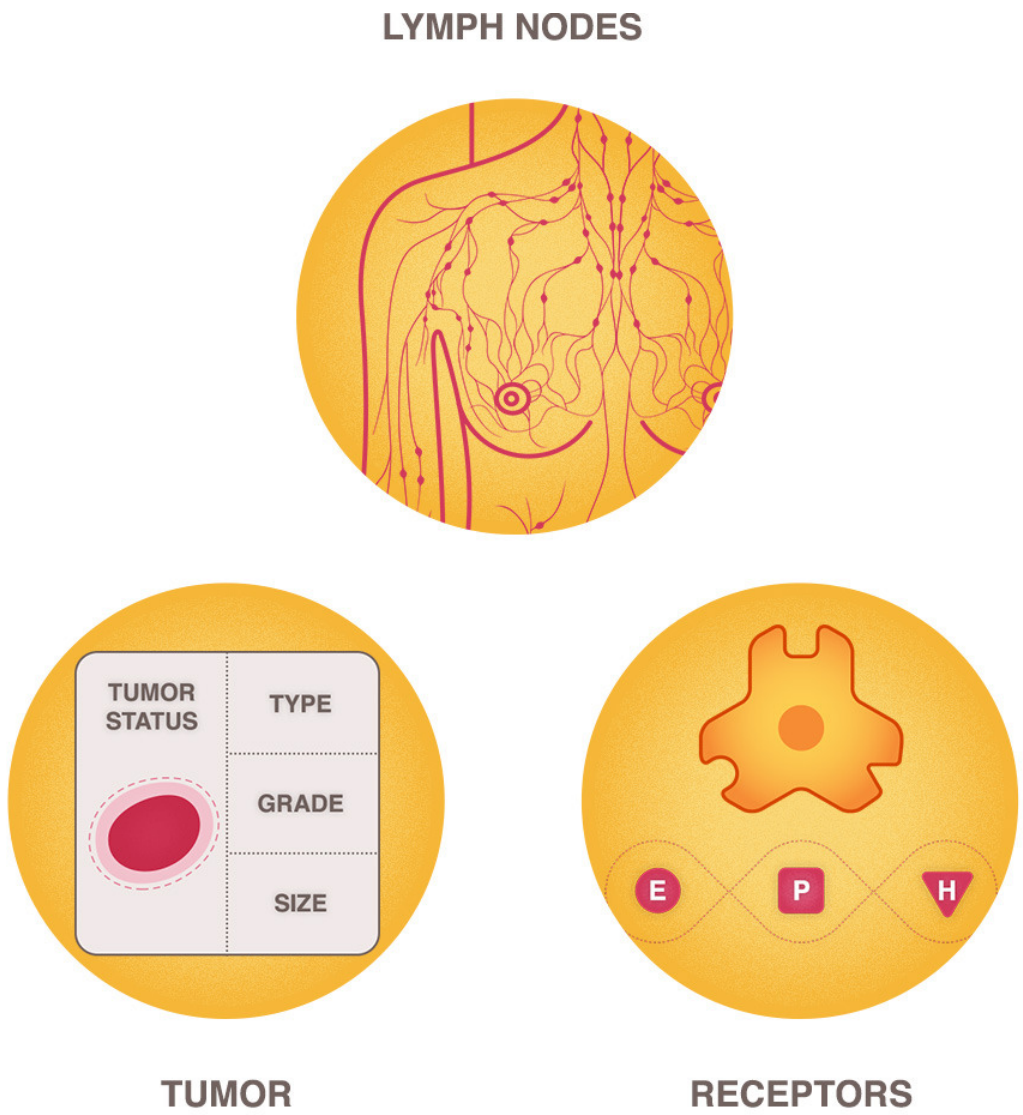
- **Work Up**
- Mammo/Ultrasound
- Core Bx- receptors- incl SISH
- +/- MRI
- Targeted scan axilla/SCF- +/-Bx.
- Consider retreatment SLN only if histol is critical to treatment decision making
- Staging
- Bloods-? incl genetic testing

-

Baseline Imaging	• Bilateral mammograms • Ipsilateral breast and axillary ultrasound • Contrast-enhanced MRI
Minimally Invasive Biopsies	• MIBB of breast and abnormal axillary node • Placement of tissue marker(s) at biopsy site(s) • Determination of tumor biomarkers (ER, PR, HER2/neu)
Consideration of NST	• Increase resectability of locally advanced breast cancer • Increase feasibility of BCS and cosmesis of Stage II & III breast cancer • Downstage axillary nodes
Systemic Staging	• Stage II: liver function studies & chest X-ray • Stage III: CT Chest abdomen +/- pelvis or PET/CT; bone scan or NaFl PET/CT • Symptom-guided imaging
Care Coordination	• Appropriate referrals to medical oncology, radiation oncology, plastic surgery, social work, etc. • Genetic counseling and testing, if indicated
Initiation of NST	• Neoadjuvant chemotherapy • Neoadjuvant endocrine therapy • Interval monitoring for tumor response, symptom management, compliance
Post-NST Imaging	• Ipsilateral mammograms • Ipsilateral breast and axillary ultrasound • Contrast-enhanced MRI
Decision for Surgery	• BCS vs. mastectomy with or without breast reconstruction • Sentinel node biopsy vs. axillary node dissection

Ann Surg Onc, 2015

Framing the discussion with the patient



4 major types of breast cancer

Hormone Receptor HR +ve
HER2 -ve
(65%)

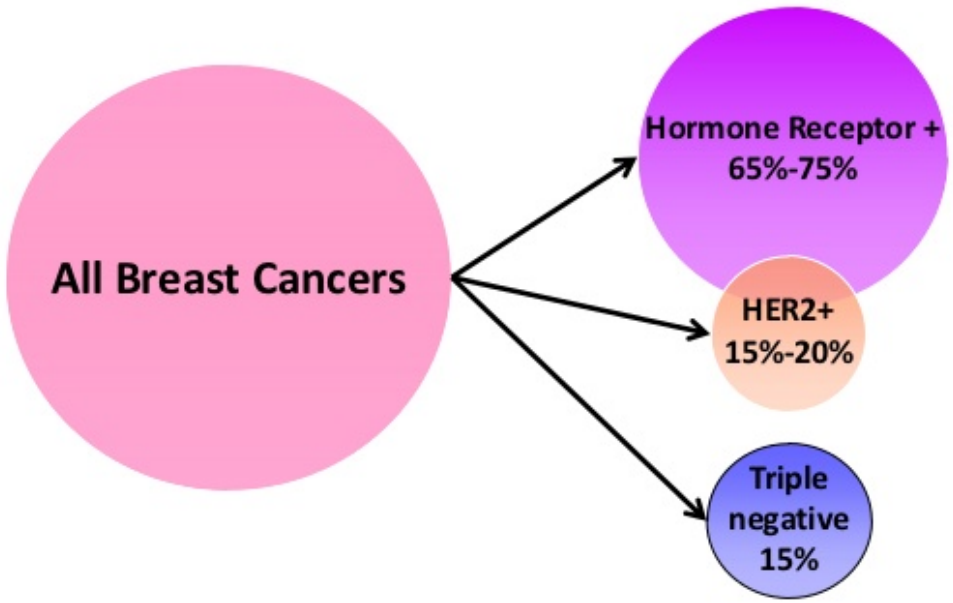
Hormone Receptor HR +ve
HER2 +ve
(10%)

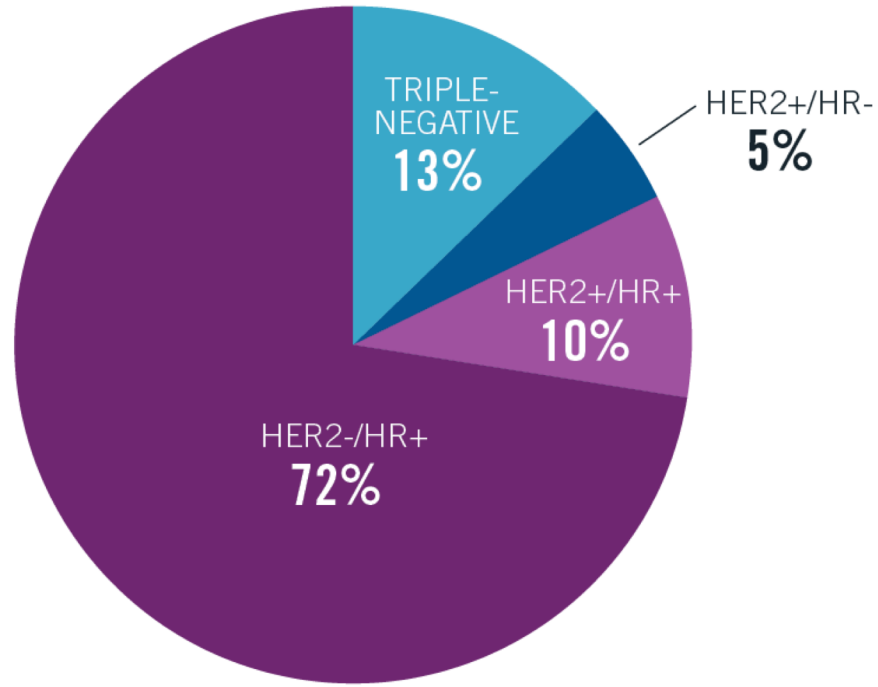
Hormone Receptor -ve
HER2 -ve
(15%)

'Triple Negative'

Hormone Receptor -ve
HER2 +ve
(10%)

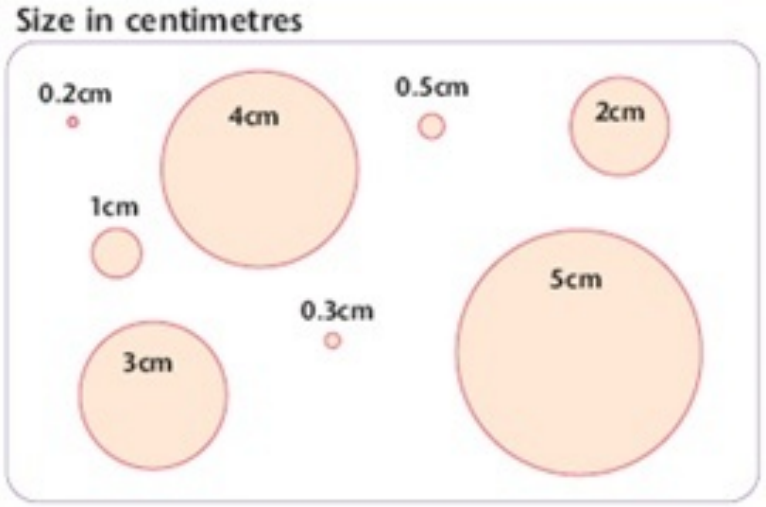
Clinical Breast Cancer Subsets

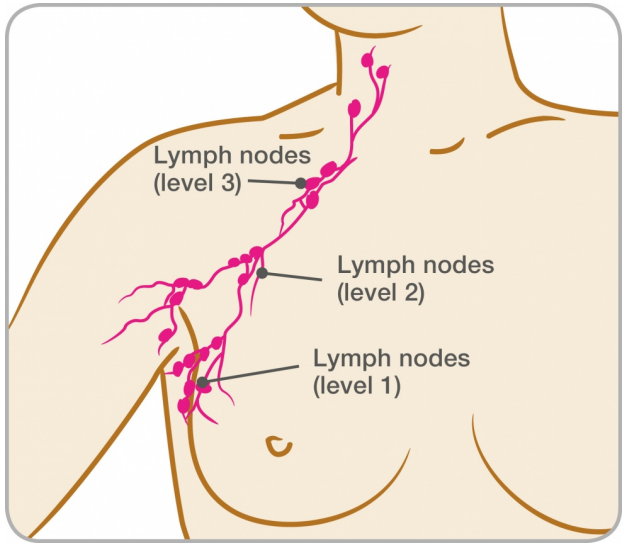




Burstein, Goldhirsch. St Gallen 2007.

Traditional Clinicopathological Features (size, nodal status and later grade)





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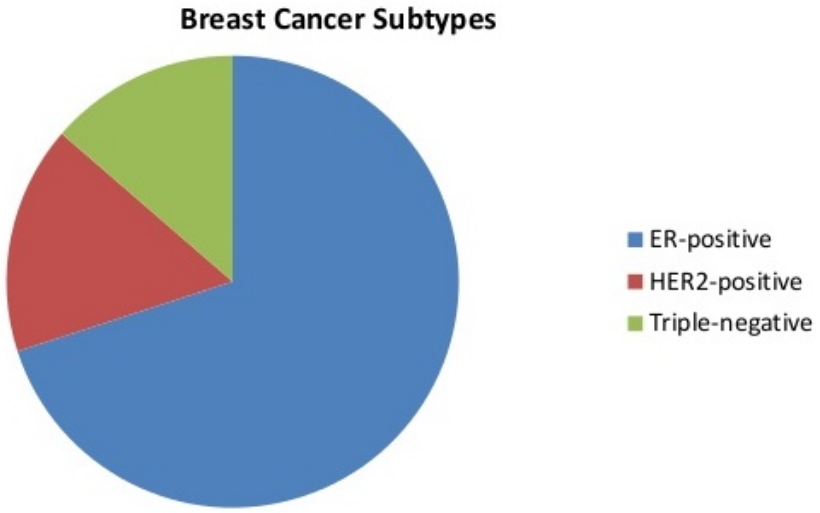
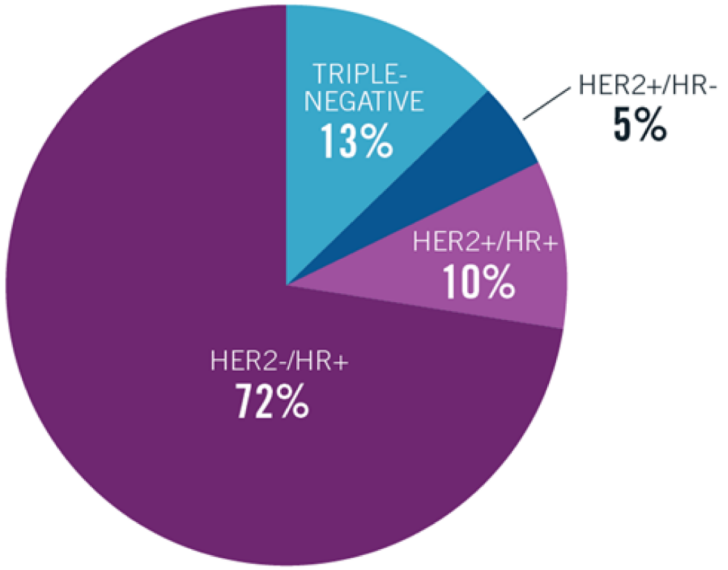
Tumour Biology





Patient Information

JAMA ONCOLOGY PATIENT PAGE

Neoadjuvant Therapy

Neoadjuvant therapy refers to any treatment that is given for cancer *before* the main treatment, with the goal of making the main treatment more likely to be successful.

What Is Neoadjuvant Therapy?

In most cancers, the primary, definitive treatment is either surgery to remove the tumor or radiation therapy to kill the tumor cells. Sometimes, extra treatment, such as chemotherapy or hormone therapy, is used either before or after the primary therapy. Extra treatment given *after* primary therapy is referred to as **adjuvant** (meaning "helper") **therapy**, whereas extra treatment given *before* primary therapy is referred to as **neoadjuvant therapy**.

This general concept of **multimodality treatment** (the use of more than 1 method to treat cancer) is often used in cancers such as breast, colon, or lung cancers. Using adjuvant or neoadjuvant therapy may improve the probability of cure.

Why Is Neoadjuvant Therapy Beneficial?

The basic concept of either neoadjuvant or adjuvant therapy is that a systemic therapy that affects the whole body, such as chemotherapy, hormone therapy, or a targeted agent, may reach cancer cells in the circulation or distant tissues that are not seen on scans or by a surgeon. These "micrometastases" have the potential to grow into visible, recurrent cancer if left untreated because they were impossible to detect earlier. In some cases, radiation therapy may also be used as neoadjuvant therapy to provide additional tumor shrinkage prior to surgery.

When Is Neoadjuvant Therapy Used?

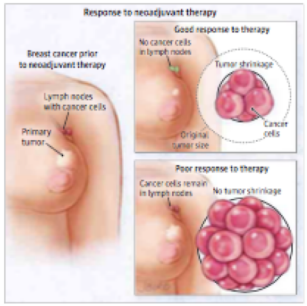
There are several reasons to use systemic neoadjuvant therapy before local definitive therapy:

- It provides treatment at the earliest opportunity, before there is a chance for micrometastases to grow while a patient receives and recovers from the local therapy.
- It may be more reliable than adjuvant therapy, particularly if local therapy is challenging and recovery is difficult. Complications can occur during local therapy that can make it difficult to give additional therapies reliably later.
- In some settings, tumor shrinkage of visible disease may make it possible to pursue a curative approach that was not possible with a larger cancer. A smaller cancer also allows for a less extensive surgery than initially required.
- It allows for measurement of systemic therapy effect on visible disease, which is correlated with long-term outcomes.

Assessing Response to Neoadjuvant Therapy

The degree of response to neoadjuvant therapy can be assessed by tumor shrinkage seen on scans, or by the extent of cancer cell death seen under the microscope from samples of the tumor and/or lymph nodes. In many cancers, a good neoadjuvant therapy is correlated with favorable survival. A **pathologic complete response**, in which there is no cancer seen in surgically removed tissue after neoadjuvant therapy, indicates a high probability of cure in many cancer settings.

Recommendations for adjuvant therapy may be based on response to neoadjuvant therapy. For example, if the first approach was less successful than hoped, a different systemic therapy may be used for adjuvant therapy.



FOR MORE INFORMATION

- Global Resource for Advancing Cancer Education (GRACE) *http://cancergrace.org/cancer-101/2015/05/18/neoadjtx/*.

To find this and other JAMA Oncology Patient Pages, go to the Patient Page link on the JAMA Oncology website at *http://www.jamaoncology.com*.

Authors: Howard (Jack) West, MD; Jill Jin, MD, MPH
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Section Editor: Howard (Jack) West, MD.

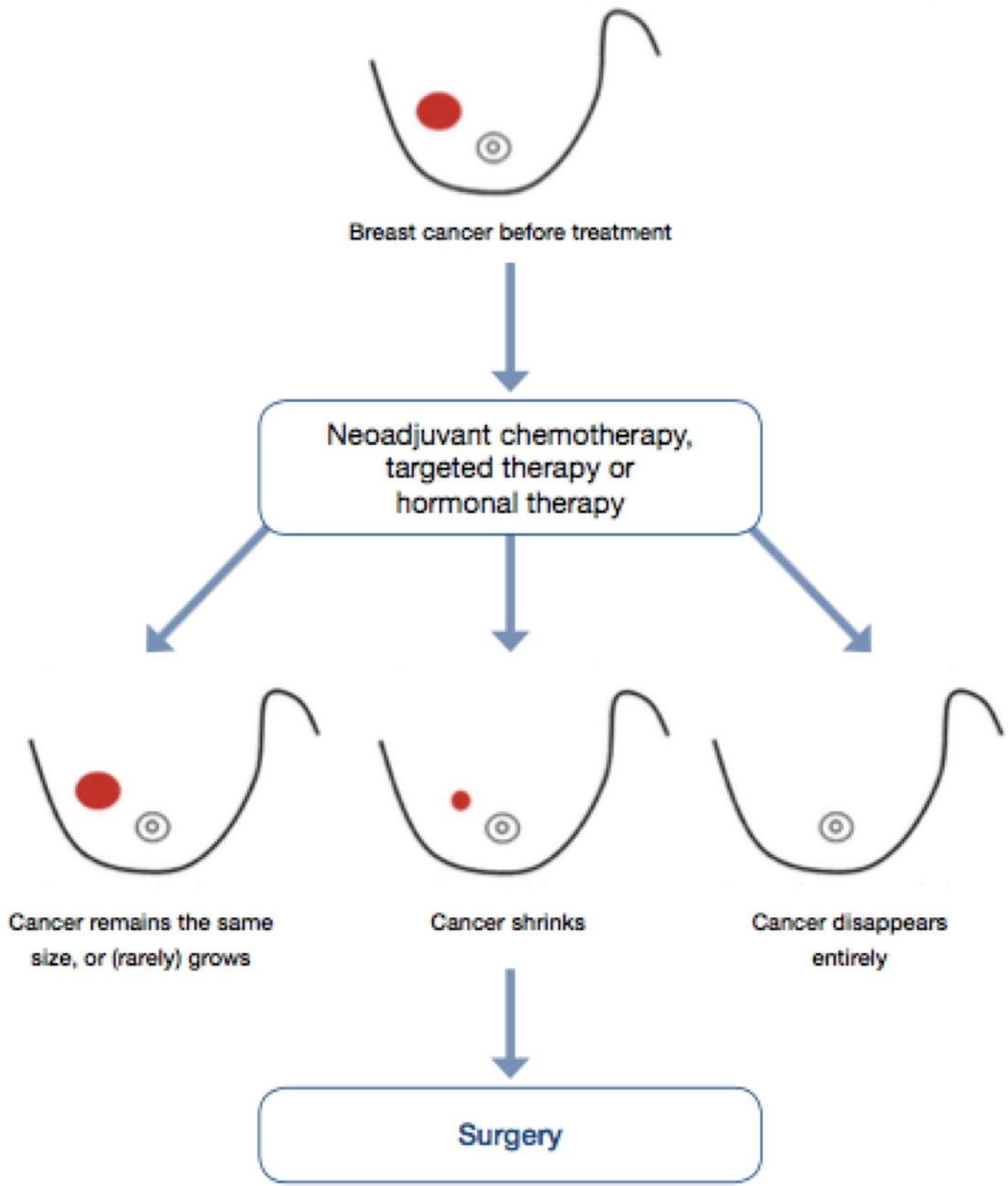
A guide for women who are considering breast cancer treatment with chemotherapy and/or hormonal therapy before surgery

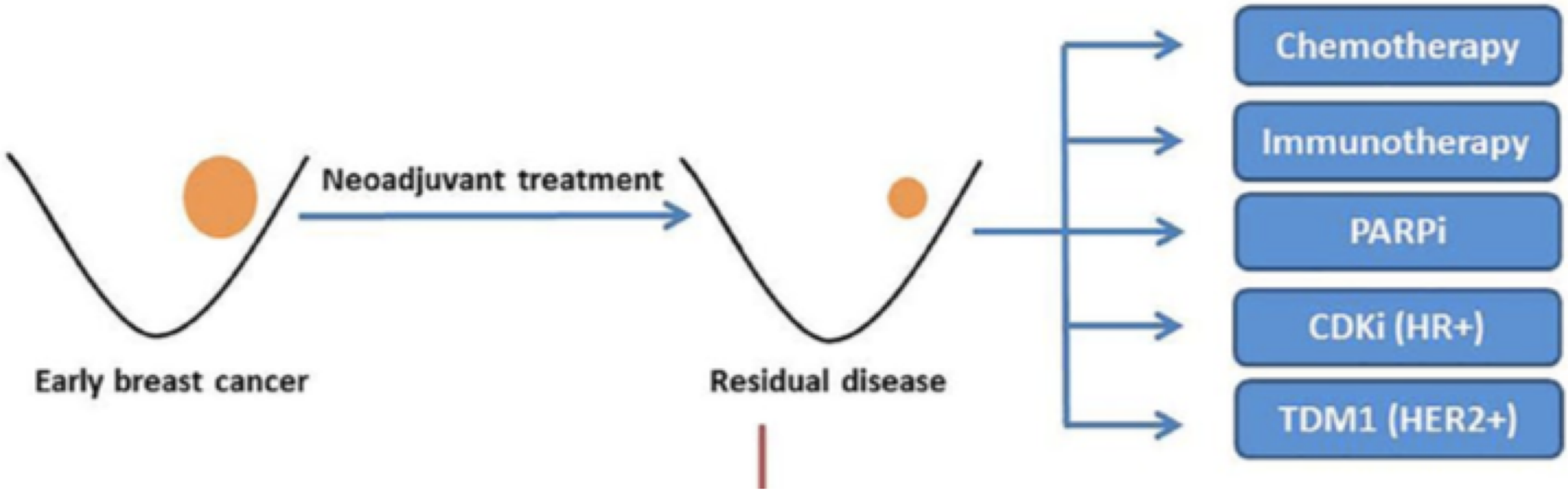
Australia & New Zealand Breast Cancer Trials Group

Chemotherapy before breast cancer surgery (neoadjuvant chemotherapy)

eviQ Cancer Treatments Online

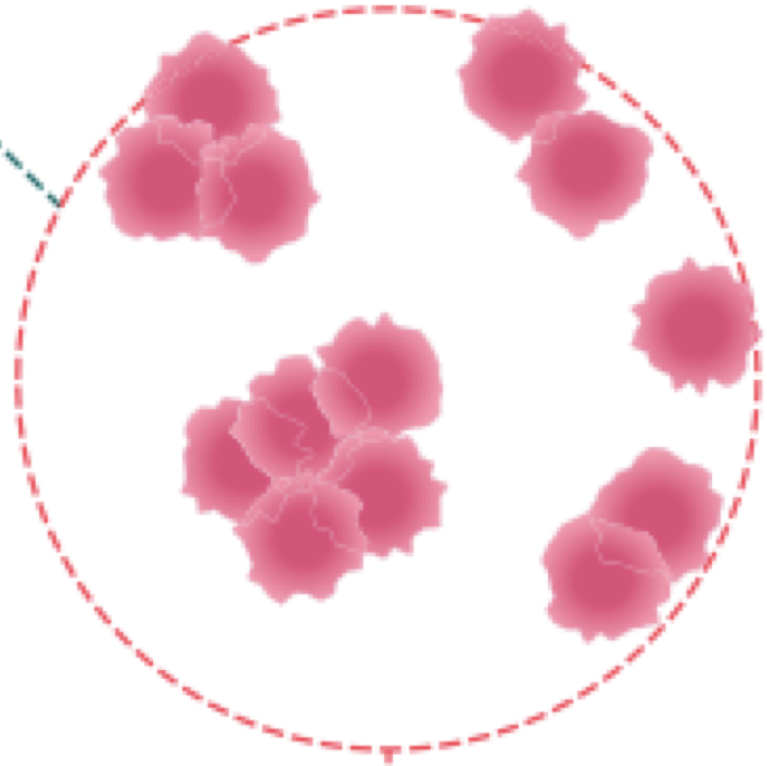
Chemotherapy given before breast cancer surgery is called neoadjuvant (nee-oh-ad-joo-vant) chemotherapy. It shrinks the lump (tumour) in the breast so it is easier to remove.


Breast cancer before treatment
Neoadjuvant chemotherapy, targeted therapy or hormonal therapy
Cancer remains the same size, or (rarely) grows
Cancer shrinks
Cancer disappears entirely
Surgery


Neoadjuvant treatment
Early breast cancer
Residual disease
Chemotherapy
Immunotherapy
PARPi
CDKi (HR+)
TDM1 (HER2+)

Response to neoadjuvant treatment:

OR



Concentric tumour shrinkage

Scattergun/Honeycomb Response

Prior to commencing NAC

Be clear to patient and document the aims of NAC in their particular circumstance

For example

- to allow time for genetic result to be avail
- To attempt downstaging for BCT
- To optimise cosmesis in the already conservable breast
- To potentially avoid ANC
- To expedite commencement systemic therapy
- To avoid post op delays in commencing adjuvant chemo
- To allow surgical planning

- Inform patient of the additional review commitments associated with NAC- if problematic- surgery first

Prior to Commencement and During NAC

- Outline the approx planned review intervals during NAC, including potential re-imaging
- Resist patient/relatives pressure to repeatedly reimage unnecessarily if clinical review is sufficient, and imaging finding will not alter surgical planning
- Indicate deadlines for surgical decision making-patients' decision making ability can deteriorate rather than improve during chemo ("chemo brain")
- I like to keep patients on a fairly short leash
- I reinforce that while regular clinical review is partly to confirm the absence of progression, progression is rare
- I now routinely emphasise that less than a CPR is not a failure, and for HER2+ and TNBC warn patients that residual disease routinely leads to a discussion of further drug therapy post op

Reasons patients gave for considering NACT:

- tumour downstaging to optimize surgery
- to observe the effect of chemotherapy on the tumour
- earlier access to highly effective systemic therapy
- to delay other decisions about breast cancer treatment such as whether to have a mastectomy or breast conserving surgery
- to plan for an immediate reconstruction
- to await genetic test results.

Barriers included:

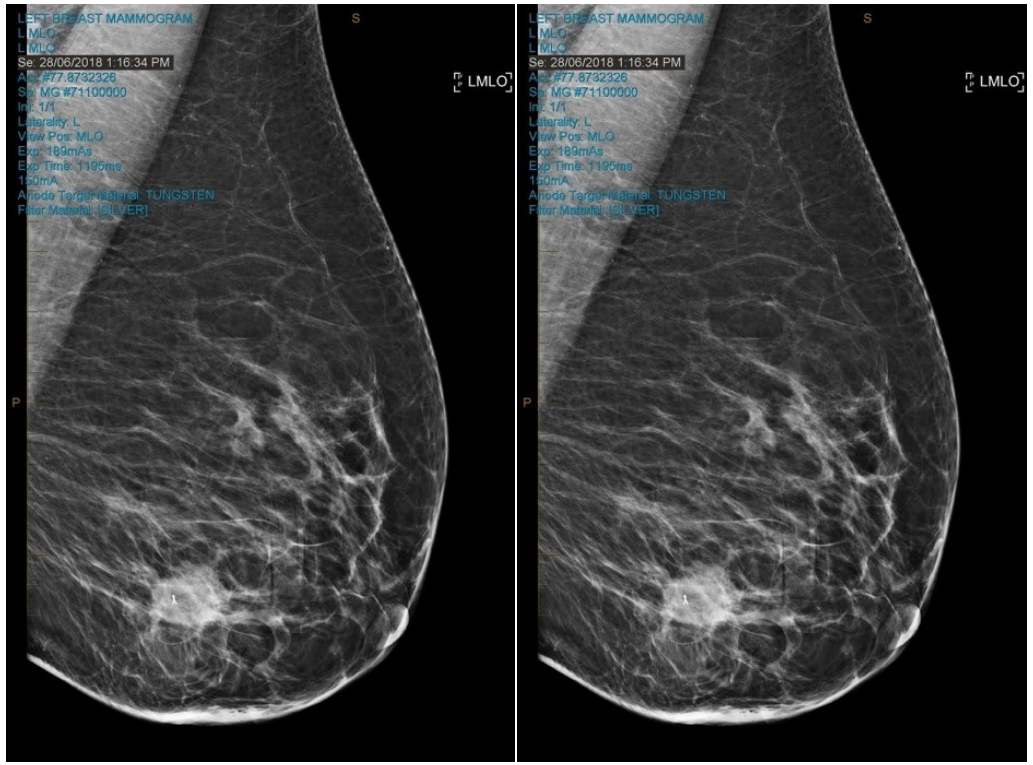
- a lack of awareness of NACT and skepticism about its validity as a standard treatment option
- prior expectation for up-front surgery
- concern that they had been offered NACT because their situation was unusual.

- Women who had not been offered NACT expressed interest in pursuing it if it had been offered.
- Some women's decision about NACT was influenced by factors unsupported by available evidence, such as fear of progression and perceived lack of efficacy.

Zdenkowski, The Breast Journal, 2015

Requirements for NAC to run smoothly

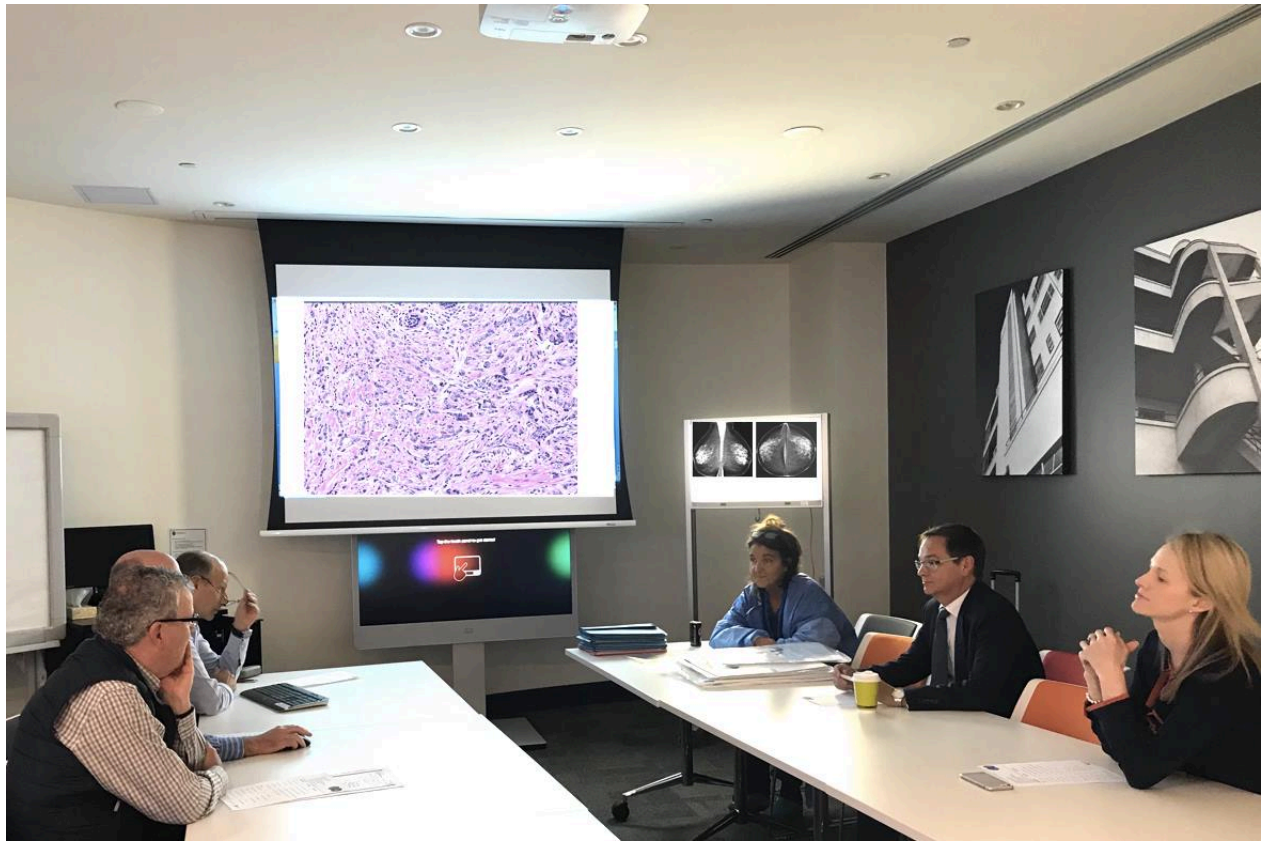
- Preop MDT, ideally attended by radiologist, incl MRI radiologist
- Good breast imaging support-placement marker clips etc
- Keen Medical Oncologist
- Prompt access to fertility specialist
- Encourage participation in prehab programme
- Plastic Surgeon

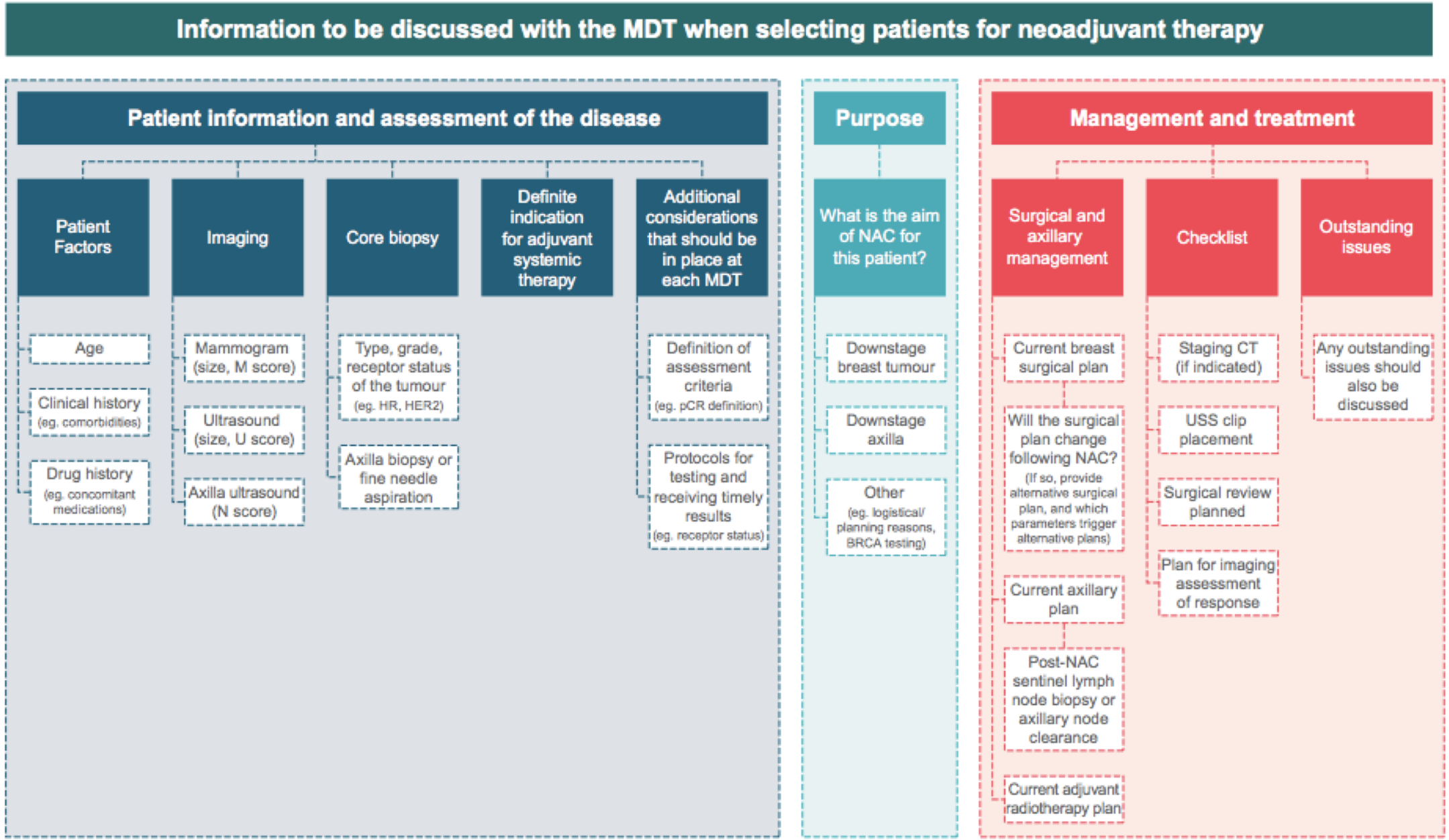


Clip inserted under ultrasound guidance

Entire Multidisciplinary Team Need to be engaged in the process

"I know we didn't accomplish anything, but that's what meetings are for."





Clinical Oncology, 2017

Monitoring DuringTreatment

- Progression in only 3%
- After decision made to proceed with NAC-book review 4-8 weeks (after 2/3 cycles AC)
- ? Plastic surgeon referral
- Genetic tests results usually avail
- **At first NAC review**: Schedule further 8 week review, often with breast imaging prior (ie after approx 2 cycles weekly Taxol)- 10 weeks to go- often able to confirm tentative surgical options
- ? Plastic surgeon referral
- **At second NAC review**: Schedule further 8 week review- ie approx 2 weeks prior to completion chemo- tentatively schedule op date for 4 weeks post completion chemo.
- **At third NAC review**: Confirm nature and date of surgery-give pt request slip for check bloods 1 week preop

Surgery

Based on:

- Extent of disease at presentation
- Patient choice
- Clinical /Imaging Response to NAC
- Genetic testing results if performed

Breast

- BCT +/-OBS
- Mx (unilat/bilat) +/- recon
- Consider need for PMRT- ie necessary / uncertain / unnecessary
- Complications increased with BMI>30, diabetes, smoking

Axilla

- ANC
- SLN- dual tracer, aim>3 nodes
- SLN+/- R/O node marked pretreatment with preop localisation

Personal Practice Audit Oct 2017-Oct 2019

- 14% of cancers underwent NAC

- 90% NAC - HER2+ 61%
  -TNBC 29%
- Remaining 10% - LABC/IBC/T4/+SCF

	% of overall Cancers	NAC	Adjuvant
HER2+	15	53	47
TNBC	7	54	46

HER2 +ve Cancers Oct 2017-Oct 2019

	NAC	Adjuvant
%	53	47
Av age (yrs)	53	53
Age Range (yrs)	39-74	34-75
Place of Residence		
Melb	45	53
Regional Victoria	43	40
Interstate	12	7

HER2 +ve Cancers Oct 2017-Oct 2019

	NAC	Adjuvant
% BCT	69	53 (25% in assoc with bilat reduction)
% Mx	31 50% recon-DIEP 50% no recon-all unilat	47 57% bilat, all but 1 recon
TNM	54% T2N1	Majority N0 40% T1N0 20%T2N0
Preop Node +ve %	79	27- mixed HER2, unsure invasive %, pt renal ca,
Chemo	92% anthracycline containing 81% Perjeta	60% TH 33% ACTH 1 pt- Aduvant Herceptin/Perjeta and subsequent Neratinib

Defining pathological complete response (pCR)

pCR in breast cancer

- pCR is the absence of cancerous cells in resected breast tissue or lymph node specimens[1]
- Patients who had a total pCR (tpCR) were not permitted in the KATHERINE trial[2]
  - Therefore, patients with residual *in situ* carcinomas only were not eligible for KATHERINE
- tpCR is the most widely accepted definition of pCR in clinical practice[3,4]

The definition of pCR can vary[1]

Commonly called	TMN code	Definition
Breast pCR (bpCR)	ypT0/is ypN0/+	Absence of invasive cancer in breast (irrespective of ductal carcinoma *in situ*). Invasive disease in lymph nodes is permitted
Total pCR (tpCR)	ypT0/is ypN0	Absence of invasive cancer in breast and axillary nodes (irrespective of ductal carcinoma *in situ*)
German Breast Group (GBG) pCR	ypT0 ypN0	Absence of invasive cancer and *in situ* cancer in breast and axillary nodes

pCR=pathological complete response

1. von Minckwitz G, *et al. J Clin Oncol* 2012; **30**:1796–1804; 2. von Minckwitz G, *et al. N Engl J Med* 2019; **380**:617–628; 3. Cortazar P, *et al. Lancet* 2014; **384**:164–172; 4. Stebbing J, *et al. Expert Rev Anticancer Ther* 2018; **18**:531-541.

Results HER2 +ve Cancers
Oct 2017-Oct 2019 undergoing NAC

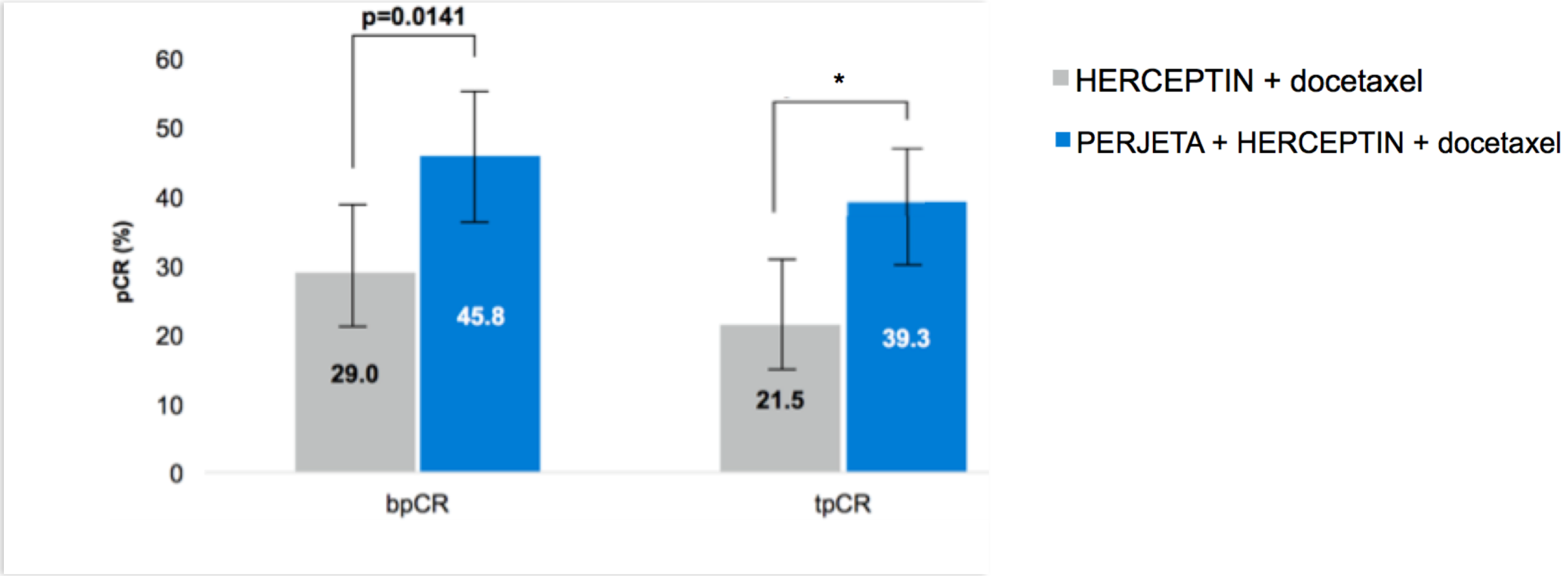
Overall Breast CPR %	71
Node -ve Breast CPR %	100
Node+ve Breast CPR %	64
Node +ve Axillary CPR	64
Non CPR % adjuvant Kadcyla	60

Table 38.3 pCR rates of combined HER2-directed therapies in the neoadjuvant setting

NeoSphere (n = 417)	*pCR (ypT0)*	
Trastuzumab + docetaxel	29.0%	
Pertuzumab + trastuzumab + docetaxel	45.8%	
Pertuzumab + trastuzumab	16.8%	
Pertuzumab + docetaxel	24.0%	
Neo-ALTTO (n = 455)	pCR (ypT0/is ypN0)	
Trastuzumab → trastuzumab + paclitaxel	29.5%	
Lapatinib → lapatinib + paclitaxel	24.7%	
Trastuzumab/lapatinib → trastuzumab/lapatinib + paclitaxel	31.3%	
TRYPHaena (n = 225)	*pCR (ypT0/is)*	*pCR (ypT0 and ypN0)*
FEC + pertuzumab + trastuzumab × 3 → pertuzumab + trastuzumab + docetaxel × 3	61.6%	50.7%
FEC × 3 → pertuzumab + trastuzumab + docetaxel × 3	57.3%	45.3%
Docetaxel/Carboplatin + trastuzumab + pertuzumab × 6	66.2%	51.9%
GeparQuinto (n = 620)	*pCR (ypT0 and ypN0)*	
Epirubicin + cyclophosphamide + trastuzumab → docetaxel + trastuzumab	30.3%	
Epirubicin + cyclophosphamide + lapatinib → docetaxel + lapatinib	22.7%	
GeparSixto (n = 137)	*pCR (ypT0 and ypN0)*	
Weekly paclitaxel + non-pegylated liposomal doxorubicin + trastuzumab + lapatinib × 18	36.8%	
Weekly paclitaxel + non-pegylated liposomal doxorubicin + trastuzumab + lapatinib × 18 + carboplatin	32.8%	
GeparSepto (n = 1.200)	*pCR (ypT0 and ypN0)*	
Weekly nab-paclitaxel × 12 → 4 × EC + trastuzumab + pertuzumab	74.6%	
Weekly paclitaxel × 12 → 4 × EC + trastuzumab + pertuzumab	66.7%	

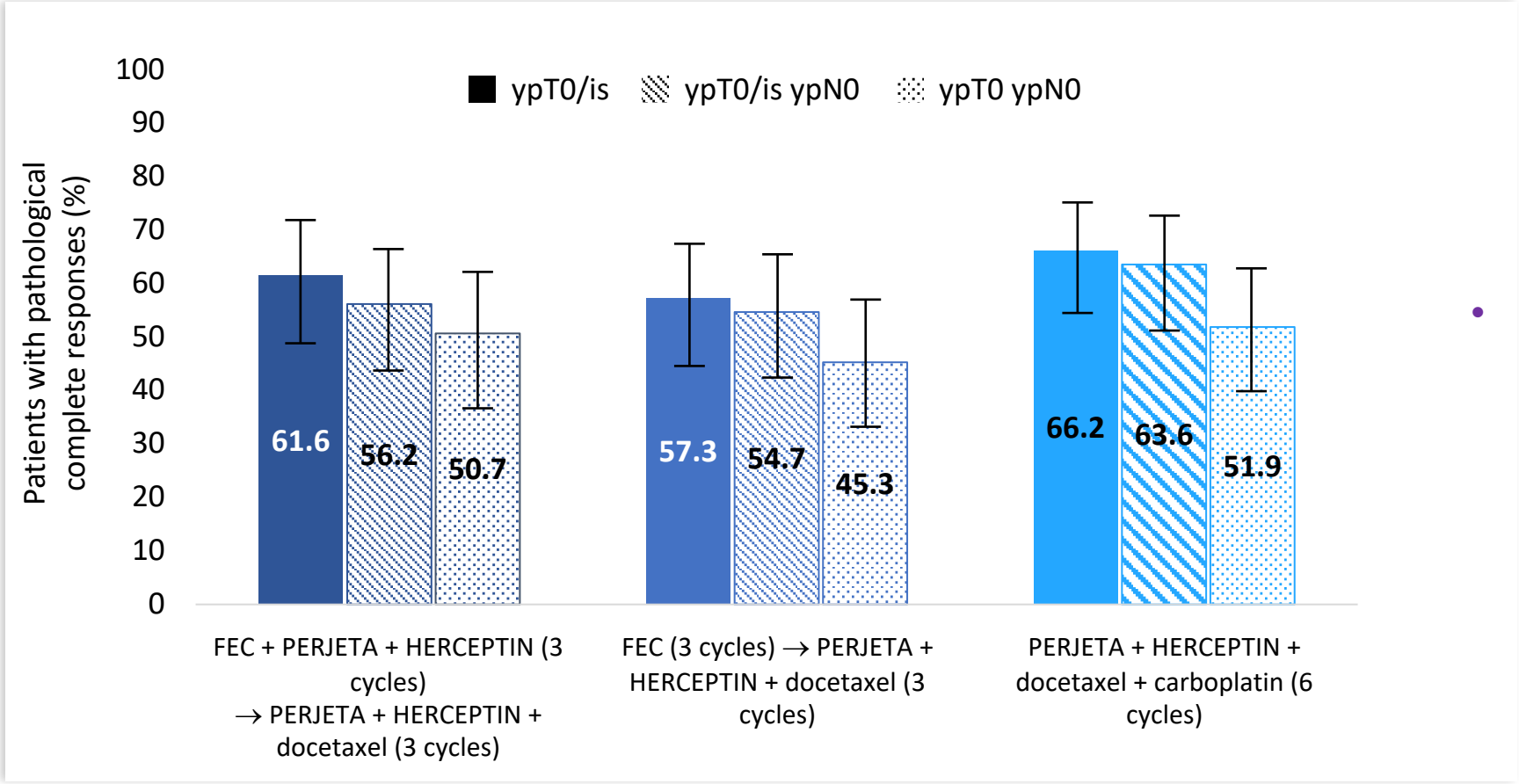
TRIAL DATA

- **NeoSphere**
- **Primary analysis of pCR rates: HERCEPTIN + docetaxel vs PERJETA + HERCEPTIN + docetaxel (ARM A vs ARM B)1,2**



- Adapted from Gianni L *et al.* 2012[1] and Gianni L *et al.* 2016.[2]
- bpCR: pCR (breast); pCR: pathological complete response; tpCR: total pCR. *p-value not stated.
- References: 1. Gianni L *et al. Lancet Oncol* 2012;13:25–32. 2. Gianni L *et al. Lancet Oncol* 2016;17:791–800.

- **TRYPHAENA**
  - **pCR rates (secondary endpoint)1**



- pCR rates support those reported in Neosphere

p-values not reported.

Adapted from Schneeweiss A *et al.* 2013[1]
FEC: 5-fluorouracil, epirubicin, cyclophosphamide.
Reference: 1. Schneeweiss A *et al. Ann Oncol* 2013;24:2278–2284.

TNBC Cancers Oct 2017-Oct 2019

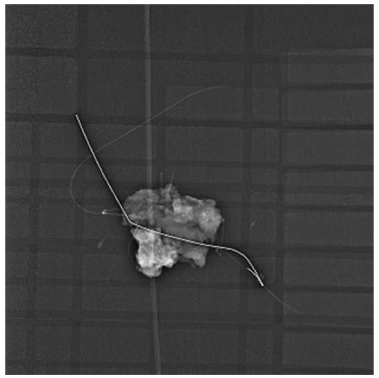
	NAC	Adjuvant
%	54	46
Av age (yrs)	50	55
Age Range (yrs)	28-68	36-67
% BCT	50	50
% Mx	50 100% bilat-2/3 recon	50 2/3 bilat 100% recon
Genetic Testing %	100 All -ve	83 50% +ve (BRCA1)
Preop Node +ve %	33	0

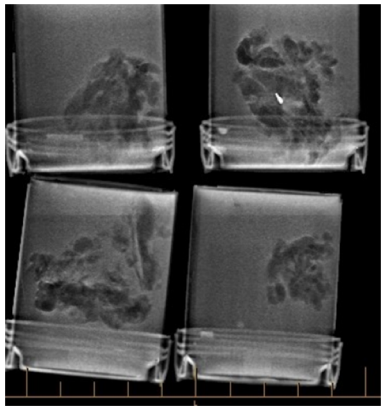
TNBC Cancers Oct 2017-Oct 2019

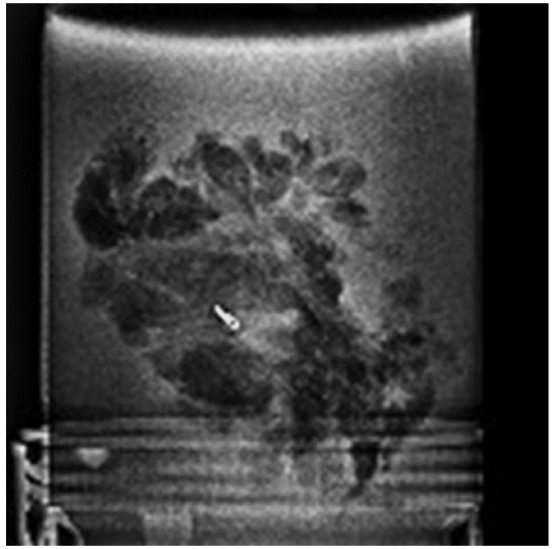
	NAC	Adjuvant
TNM	2/3 -T2N0 1/3 -T2N1	2/3 - T2N0 1/3 - T1N0
Chemo	All AC/T	2/3 ACT (T2N0) 1/3 TC (T1N0)
CPR	16%	-
Non CPR % Xeloda	60	-

Lessons learnt from experience

- Consider what is the most appropriate treatment sequencing in all breast cancer diagnoses
- Start framing the treatment sequencing discussion early with the patient
- Discuss all patients in preop MDM, especially possible candidates for NAC
- Be clear to patient and document the "aims" of NAC in particular circumstance
- Indicate and adhere to deadlines for surgical decision making- more time does not automatically equate to high quality, informed decision making
- If clip not in nodal hookwire specimen- xray sentinel nodes







Lessons learnt from experience

- In HER2+ve breast cancer, trial results can be replicated in practice, with high rates of CPR in breast and axilla achievable
- Emphasise that less than a CPR is not a failure of treatment
- For HER2+ and TNBC warn patients that residual disease routinely leads to a discussion of further drug therapy post op
- Patients who do not achieve a CPR are interested in pursuing additional "adjuvant" therapy (60% of both HER2+ve and TNBC)
- Patients want to be informed about non PBS funded drugs*, and many elect to self fund (Fellowfield et al, 2011)

For pts undergoing NAC for HER2+ BC between Oct 2017-Oct 2019:

- 81% pts self funded neoadjuvant Perjeta
- 60% pts with residual disease elected to self fund Kadcycla*

* avail on PBS April 1st 2020

Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019

H. J. Burstein[1*†], G. Curigliano[2*†], S. Loibl[3], P. Dubsky[4], M. Gnant[5], P. Poortmans[6,7], M. Colleoni[2], C. Denkert[8], M. Piccart-Gebhart[9], M. Regan[10], H.-J. Senn[11], E. P. Winer[1‡], B. Thurlimann[11‡] & Members of the St. Gallen International Consensus Panel on the Primary Therapy of Early Breast Cancer 2019[§]

International guidelines now recommend:

- **Consideration of adding neoadjuvant pertuzumab**
- **Patients with residual disease "should" receive adjuvant Kadcyla**

Neoadjuvant therapy	Neoadjuvant systemic therapy (NST) is the preferred initial approach in women with stage 2 or 3, HER2-overexpressing or triple-negative breast cancer NST increasingly enables selected women to avoid axillary dissection surgery, sparing women loss of function and lymphedema NST increasingly enables tailored approaches to therapy in TNBC and HER2-positive breast cancer that can improve long-term outcomes for women with breast cancer

- Neoadjuvant systemic therapy (NST) is the preferred initial approach in women with stage 2 or 3, HER2-overexpressing or triple negative breast cancer
- NST increasingly enables selected women to avoid axillary dissection surgery, sparing women loss of function and lymphoedema
- NST increasingly enables tailored approaches to therapy in TNBC and HER2-positive breast cancer that can improve long-term outcomes for women with breast cancer

HER2+ and TNBC adjuvant therapy	Women with stage 2 or 3 HER2-positive breast cancer should consider adding pertuzumab in addition to trastuzumab Women with HER2-positive and residual tumor after NST should receive trastuzumab emtansine therapy in the adjuvant setting Women with triple-negative breast cancer and residual tumor after NST should consider capecitabine in the adjuvant setting

- Women with stage 2 or 3 HER2-positive breast cancer should consider adding pertuzumab in addition to trastuzumab
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Annals of Oncology, 2019

?? The Future

EDITORIAL – BREAST ONCOLOGY

Omitting Surgery in Complete Responders After Neoadjuvant Chemotherapy: The Quest Continues

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The Breast Centre